**APPLICATION**

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**FOR**

# UNITED STATES PATENT

**ON**

# CONFIGURABLE DYNAMIC THREE DIMENSIONAL ARRAY



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Sheets of Drawings (5)

# CONFIGURABLE DYNAMIC THREE DIMENSIONAL ARRAY

## BACKGROUND OF THE INVENTION

Throughout this application various publications are referenced within parentheses. The disclosures of these publications in their entireties are hereby incorporated by reference in this application in order to more fully describe the state of the art to which this invention pertains.

### 1. Field of the Invention

The present invention relates generally to arrays of probes. In particular, the invention relates to a system and method using a plurality of optical traps to form a configurable dynamic array of probes which may or may not be substrate bound.

### 2. Discussion of the Related Arts

Arrays of potentially reactive probes have a long history of use in assays and other chemical and biological tests and experiments. For example, arrays are often used in the fields of genetics, biochemistry, and biology to assay a sample for biological or chemical material (known as a target). Often the sample being assayed is only available in relatively small quantities. This limited availability of some materials led to the development of microarrays useful to present a relatively high density of probes, in a small array, to assay for targets in a small quantity of a sample.

Microarrays used in the testing of biological material are often referred to as bio-chips. Two principal applications of bio-chips are: extraction of sequence information about a specific nucleic acid, i.e., whether that nucleic acid corresponds to an organism's entire genome, a single gene, or a portion of a single gene (U.S. Patent No. 6,025,136); and evaluation of gene expression. (See *Schena, M. et al.* "Quantitative monitoring of gene expression patterns with a complimentary DNA microarray," Science 270 (5235):467-70 (Oct. 20, 1995); *D.J. and Winzeler, E.A.*, "Genomics, gene expressiona and DNA arrays," Nature 405(6788):827-836 (2000) and *Ekins, R. and Chu, F.W.*, "Microarrays: their origins and applications," Trends in Biotechnology 17:217-18 (1999).)

Conventional microarrays are comprised of either a linear or a two-dimensional configuration of oligonucleotide probes, attached to the planar surface of a solid support (substrate). Different types of oligonucleotides are affixed to the substrate at predetermined

locations. Consequently, once the microarray is formed, the location of the probes and hence the location of any targets that react with the probes is always known. The attachment of the probe is achieved by either direct synthesis of the oligonucleotide onto the substrate through a process known as *in situ* photolithography synthesis (U.S. Patent Nos. 5,837,832 and 5,143,854), or attachment of the oligonucleotide after it has been synthesized.

One drawback of such microarrays is that their linear or two dimensional configuration provides a limited surface area to which probes can be attached, thereby setting a limit on the density of the probes to assay for the targets. In the case of DNA hybridization between targets (DNA or DNA fragments) and probes (immobilized oligonucleotides) the rate of hybridization is controlled by the rate at which the targets are able to pass into contact with the probes. Accordingly, the higher the density of probes, the greater the rate of hybridization.

A second drawback of such microarray stems from the method of their configuration. Once a microarray is fabricated, the type and quantity of the probes become fixed.

In an alternative approach to assaying for targets in a small quantity of a sample, probes are affixed to the surface of small bead-like substrates. (WO 00/61198 pending for *Kambara & Mitsuhashi.)* Each bead containing a different probe is marked with a distinct label, thus permitting the identification of each probe and bound target by discerning which bead has what label after completion of the assay (See WO 00/71243).

The identity of the bead and probe is maintained by physically transferring the bead with probe attached into a guide, capillary tube, groove, or holes within a sheet, then washing the beads with targets. While the non-flat nature of the beads does provide greater surface area for the targets to interact, than does a microarray probe, the beads must still be held in some pre-determined order throughout the assay to maintain a record of the identity of what bead is supporting which probe or the bead probes must be collected and each bead probe examined, after the assay, to determine its identity.

An additional drawback of both the microarray and the bead assays is the required physical attachment of the probe to a substrate. In some instances the attachment will in and of itself alter the probe, or effect the process that the probe is being used to assay. In other instances, during or after the initial assay information may be obtained that would make for desirable alterations of the quality or quantity of the probes, if the identity of the probes was

both known throughout the assay and the configuration of the array could be easily altered. However, such alterations are not possible with either the microarray or bead assays.

In an unrelated art, it is known to optical trap particles with multiple simultaneously generated optical tweezers. (See generally U.S. Patent No. 6,055,106 issued to *Grier & Dufresne*.) Optical tweezers use the gradient forces of a focused beam of light to trap particles based on the dielectric constant of a particle. To minimize its energy, a particle having a dielectric constant higher than the surrounding medium will move to the region of an optical tweezer where the electric field is the highest.

Alternatively, stated in terms of momentum, the focused beam of light produces radiation pressure, creating small forces by absorption, reflection, diffraction or refraction of the light by a particle. The forces generated by radiation pressure are almost negligible--a light source, such as a diode-pumped Nd:YAG laser operating at 10mW, will produce a force of only a few picoNewtons. However, a few picoNewtons of force is sufficient to trap small particles having dielectric properties.

Other optical tools that can be used to optically trap particles include, but are not limited to, optical vortices, optical bottles, optical rotators and light cages. An optical vortex produces a gradient surrounding an area of zero electric field which is useful to manipulate particles with dielectric constants lower than the surrounding media or which are reflective, or other types of particles which are repelled by an optical tweezer. To minimize its energy such a particle will move to the region where the electric field is the lowest, namely the zero electric field area at the focal point of an appropriately shaped laser beam. The optical vortex provides an area of zero electric field much like the hole in a doughnut (toroid). The optical gradient is radial with the highest electric field at the circumference of the doughnut. The optical vortex detains a small particle within the hole of the doughnut. The detention is accomplished by slipping the vortex over the small particle along the line of zero electric field.

The optical bottle differs from an optical vortex in that it has a zero electric field only at the focus and a non-zero electric field at an end of the vortex. An optical bottle may be useful in trapping atoms and nanoclusters which may be too small or too absorptive to trap with an optical vortex or optical tweezers. *(J. Arlt and M.J. Padgett.* "Generation of a beam with a dark focus surrounded by regions of higher intensity: The optical bottle beam," Opt. Lett. 25, 191-193, 2000.)

The optical rotator is a recently described optical tool which provides a pattern of spiral arms which trap objects. Changing the pattern causes the trapped objects to rotate. *(L. Paterson, M.P. MacDonald, J. Arlt, W. Sibbett, P.E. Bryant, and K. Dholakia*, "Controlled rotation of optically trapped microscopic particles," Science 292, 912-914, 2001.) This class of tool may be useful for manipulating non-spherical particles and driving MEMs devices or nano-machinery.

The light cage, (*Neal* in U.S. Patent No. 5,939,716) is loosely, a macroscopic cousin of the optical vortex. A light cage forms a ring of optical vortices to surround a particle too large, too reflective, or with dielectric constants lower than the surrounding media. If the optical vortex is like a doughnut, the light cage is like a jelly-filled doughnut. While the doughnut hole (for the vortex) is an area of zero electric field, the jelly-fill is an area of lowered electric field. In a gross sense, the gradient forces of the plurality of optical tweezers forming the doughnut "push" a particle, with a dielectric constant lower than the surrounding medium, towards the jelly-fill which may also be thought of as the less bright region which lies between the plurality of optical tweezers. However, unlike a *vortex*, no-zero electric field area is created . An optical vortex, although similar in use to an optical tweezer, operates on an opposite principle.

There exists a need for an assay method and system in which the interaction of the probes and targets can be evaluated absent attachment of the probe to a substrate. There also exists a need for a method and system of forming an array of probes which is configurable (and re-configurable), the method maintaining the identity of the probes throughout the assay irrespective of the location of the probe. The present invention satisfies these and other needs, and provides further related advantages.

## SUMMARY OF THE INVENTION

The present invention provides a novel and improved method and system to construct, configure and use a three dimensional array of probes.

Within a vessel optical traps are generated. The optical traps are produced by passing a focused beam of light such as a laser beam, through a beam altering optical element, to generate beamlets. The beamlets in turn are focused through a lens and produce the gradient conditions necessary for optical trapping. Probes, each with a known characteristic, are then

added to the vessel. The probes for a given assay are chosen and then each is selected by containing it within an optical trap.

The quantity and quality of probes forming the array are readily re-configurable by using the optical traps to add, discard, or replace probes. The arrangement of the probes, in the array, relative to one another is also dynamic because the spatial relationship of the probes to one another can be altered while maintaining the identity of the selected probes from which the array was configured. Accordingly, both the array and each of its probes are also movable in three dimensions and can be positioned, moved and re-positioned as a whole, or separately within the vessel.

While a probe remains contained within an optical trap, regardless of whether it has been repositioned within the vessel and regardless of any change in it spatial position "order" in the array, the identity of the probe can be maintained by virtue of knowing the identity of the optical trap by which the probe is contained. Additionally, one optical trap can pass the probe to another optical trap and so on, while tracking the chain of optical trap custody of the probe thereby maintaining the identity of what probe is contained by which optical trap.

Other features and advantages of the present invention will be set forth, in part, in the descriptions which follow and the accompanying drawings, wherein the preferred embodiments of the present invention are described and shown, and, in part, will become apparent to those skilled in the art upon examination of the following detailed description taken in conjunction with the accompanying drawings, or may be learned by practice of the present invention. The advantages of the present invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appendant claims.

## DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates a partial cut-away side view of a system forming an array of configurable probes.

FIG. 2 illustrates a view of a free-probe contained within an optical trap.

FIG. 3 illustrates an overview of a system for forming an array of probes.

FIG. 4 illustrates a beam altering element with multiple static regions.

FIG. 5A illustrates a first operative movement of probes.

FIG. 5B illustrates a second operative movement of probes.

FIG. 6A illustrates a component view of a compact system to form optical traps.

FIG. 6B illustrates an inverted microscope to which the compact system of Fig. 6A attaches.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Particular embodiments of the invention are described below in considerable detail for the purpose of illustrating its principles and operation. However, various modifications may be made, and the scope of the invention is not limited to the exemplary embodiments described below. For example, while specific reference is made to biological systems and assays for gene sequencing and DNA hybridization, it can be appreciated that the method and system is of equal utility in such areas as optical circuit manufacturing and testing, nanocomposite material construction and testing, fabrication of opto-electronics, electronic components and testing, assembly and testing of holographic data storage matrices, chemical assays, genomic assays, proteomics assays, facilitation of combinatorial chemistry, promotion of colloidal self-assembly, probing non-biological materials. Certain terminology will be used in the following specification, for convenience and reference and not as a limitation, brief definitions are provided below:

A. "*Beamlet*" or "*beamlets*" refers to a sub-beam of focused light or energy that is generated by directing a focused beam of light or energy, such as that produced by a laser or collimated output from a light emitting diodes, through a media which diffracts it into two or more sub-beams. An example of a beamlet would be the higher order laser beams diffracted off of a grating.

B. "*Phase profile* " refers to the phase of light or energy in a cross-section of a focused of light or energy beam or a beamlet.

C. "*Phase pattern*" refers to a patterned phase shift imparted to a focused beam of light or energy or a beamlet which alters its phase profile, including, but not limited to, phase modulation, mode forming, splitting, converging, diverging, shaping and otherwise steering a focused beam of light, energy or a beamlet.

FIG. 1 illustrates an array 8 of substrate-bond probes 500-504 for assaying a biological material. The probes are configured within a subject cell 10 using optical traps 1000-1004 constructed from focused beamlets 2000-2004 emanating from a focusing lens 12. The subject cell 10 is a vessel constructed of a substantially transparent material which allows the beamlets to pass through and which does not interfere with the formation of the optical traps.

The focused *beamlets* 2000-2004 form the optical traps 1000-1004 by producing the gradient conditions necessary to contain and manipulate small particles in three dimensions. Only five sets of probes, beamlets and optical traps are shown for clarity, but it should be understood that a greater or lesser number can be provided depending on the nature, scope and other parameters of the assay and the capabilities of the system producing the optical traps.

When assaying biological material the term "probe", as used herein, refers to a biological or chemical material that selectively binds to, or reacts with, a target. Probes include, but are not limited to, oligonucleotides, polynucleotides, chemical compounds, proteins, peptides, lipids, saccharides, ligands, cells, antibodies, antigens, cellular organelles, lipids, blastomeres, aggregations of cells, microorganisms, cDNA, RNA and the like.

A "target", as used herein, refers to a biological or chemical material whose presence or absence in a sample is desired to be detected by binding to or reacting with a probe. Typically the presence of the material is detected by a reaction such as a hybridization of the genetic material of the target to a probe. Target materials also include, but are not limited to oligonucleotides, polynucleotides, chemical compounds, proteins, lipids, saccharides, ligands, cells, antibodies, antigens, cellular organelles, lipids, blastomeres, aggregations of cells, microorganisms, peptides, cDNA, RNA and the like.

Prior to performing an assay, probes which posses particular binding and/or reacting characteristics are chosen for an assay. The optical traps are then used to select the probes by containing the probes within the optical traps. A group of such contained probes are thereby configured to form an array.

The probes 500-504 may be bound to any suitable substrate. An important characteristic of a suitable substrate is that it be a material which can be contained by, and manipulated with, an optical trap. Representative substrates includes beads, irregular small particles, or other regular small particles. Suitable substrates are constructed of materials which include, but are not limited to, control pore glass, ceramics, polystyrene, methylstyrene, acrylic polymers, paramagnetic materials, thoriosol, carbon graphite, titanium dioxide, latex, or cross-linked dextrans such as sepharose, cellulose, nylon, cross-linked micelles, teflon, and plastic.

As shown in FIG. 2, the method of the instant invention also includes using one or using more optical traps 1005 (one shown) to contain one or more probes 505 (one shown) that are unbound to a substrate. It should be understood that the configurable arrays may contain only bound probes, only unbound probes, or a combination of bound and unbound probes. Selection of what mixture, if any, of bound and unbound probes may in part be influenced by a probe's physical properties. Specifically, the properties of certain probes, such as skin cells, may be altered, absent adhesion to a substrate. Conversely, the action of other probes, such as proteins, may be better served by maintaining the tertiary structure of the probe/protein by eliminating the substrate.

In some embodiments, the substrate is labeled with a marker (such as a wavelength specific dye, color, and the like to facilitate identification of the probe for inclusion in an array. If the substrate of the probe is labeled with a wavelength specific marker, the selection of probes 500-504 may be accomplished by adding the labeled probes to the subject cell 10 in an unspecified order, then using spectral measurement as illustrated in (FIG. 3) of the probe's substrate to direct an optical trap to select or not select a particular probe for inclusion in the array. If unlabeled probes are chosen to form part of the array, to maintain identification of the unlabeled probes, the probes can be added to the subject cell 10 in a sequential order and acquired in a corresponding sequence by the optical traps. Alternatively, labeled or unlabeled probes may be placed in a series of sub-cells 16 (one shown), within the subject cell 10. Placement may be by any suitable means including movement by optical traps, flow channels, micro-capillaries and other similar mechanisms.

In FIG. 1, for clarity, only one sub-cell 16 is shown. However, it should be understood that a plurality of such sub-cells can be provided. In each sub-cell one or more probes, all with common known characteristics can be placed, thereby providing a selection

of probes of different quality for array constructing, configuration and re-configuration. In some instances it may be necessary or desirable to construct the boundaries of a sub-cell with optical traps. The appropriate number of optical traps placed in the right orientation can create an optical sub-cell which performs the same functions as the physical sub-cell 16.

To perform an assay, a first batch of targets T1-T5 are added to the subject cell 10, which also contains a fluid media 3000, via an inlet port 14 which communicates with the subject cell 10. The probes are suspended in the media 3000 via their containment by the optical traps. To increase the opportunity for interaction with the targets, the probes may also be moved about the subject cell corresponding to movement of the optical traps. Additionally, any given probe in the array may be independently re-positioned within the subject cell and the identity of each probe remains known by the optical trap in which it is contained, irrespective of where the optical trap positions the probe. Accordingly, both the probes forming the array and the locations of probes forming the array may be altered and hence configured and re-configured.

Illustrated in FIG. 3 is an overview of a system to generate and control a configurable array, generally designated as 20. Optical traps 1000-1004 (FIG. 1) are formed by passing a collimated light, preferably a laser beam 100, produced by a laser 102 to a beam splitter 30. The beam splitter 30 is constructed of a dichroic mirror, photonic band gap mirror, omnidirectional mirror, or other similar device. The beam splitter 30 selectively reflects the wavelength of light used to form the optical traps and transmits other wavelengths. A portion of the reflected light is then passed through a beam altering optical element 22 disposed substantially in a plane 24 conjugate to a planar back aperture 28 of the focusing lens 12 into the subject cell 10.

Any suitable laser can be used as the source of the laser beam 100. Useful lasers include solid state lasers, diode pumped lasers, gas lasers, dye lasers, alexanderite lasers, free electron lasers, VCSEL lasers, diode lasers, Ti- Sapphire lasers, doped YAG lasers, doped YLF lasers, diode pumped YAG lasers, and flash lamp-pumped YAG lasers. Diode-pumped Nd:YAG lasers operating between 10 mW and 5 W are preferred.

When the laser beam 100 is directed through the beam altering optical element 22, the beam altering optical element produces a plurality of beamlets having an altered phase profile. Depending on the number and type of optical traps desired, the alteration may include diffraction, wavefront shaping, phase shifting, steering, diverging and converging.

Thus, the laser beam 100 proceeds from area A' on the beam splitter 30 to area A on the beam altering optical element 22 and through area B at the back aperture 28 aperture of the focusing lens 12 thereby effectively overlapping all the *beamlets* at the back aperture of the focusing lens. The *beamlets* are then converged as the pass through the focusing lens 12 thereby producing the optical gradient conditions necessary to form the optical traps.

Suitable beam altering optical elements are characterized as transmissive or reflective depending on how they direct the focused beam of light or energy. Transmissive diffractive optical elements transmit the beam of light or energy, while reflective diffractive optical elements reflect the beam.

A beam altering optical element can also be categorized as being static or dynamic. Examples of suitable static beam altering optical elements include those with one or more fixed surface regions, such as gratings, holograms, stencils, light shaping holographic filters, polychromatic holograms, lenses, mirrors, prisms, waveplates and the like. The static beam altering optical element 40, as shown in FIG. 4, is characterized by a fixed surface 41. However, the surface may itself be movable, thereby allowing for the selection of one more of the fixed regions 42-46 by moving the beam altering optical element relative to the laser beam to select the appropriate region. The static beam altering optical element may be attached to a spindle 47 and simply rotated with a controlled electric motor (not shown).

Examples of suitable dynamic beam altering optical elements having a time dependent aspect to their function include computer generated diffractive patterns, phase shifting materials, liquid crystal phase shifting arrays, micro-mirror arrays, piston mode micro-mirror arrays, spatial light modulators, electro-optic deflectors, accousto-optic modulators, deformable mirrors, reflective MEMS arrays and the like. With a dynamic beam altering optical element, the media which comprises the beam altering optical element can be altered, to change the phase pattern imparted to the focused beam of light which results in a corresponding change in the phase profile of the focused beam of light, such as diffraction, or convergence.

Preferred dynamic optical elements include phase-only spatial light modulators such as the "PAL-SLM series X7665", manufactured by Hamamatsu, of Japan or the "SLM 512SA7," manufactured by Boulder Nonlinear Systems of Layafette Colorado. These beam altering optical elements are computer controlled to generate the beamlets 2000-2004 (FIG. 1).

The beam altering optical element is also useful to impart a particular topological mode to the laser light. Accordingly, one *beamlet* may be formed in a Guass-Laguerre mode while another *beamlet* formed in a Guassian mode.

The beam splitter 30 also provides a light beam 32 forming an optical data stream, aided by imaging illumination 39 which passes through the subject cell 10 to be viewed, converted to a video signal, monitored, or analyzed by visual inspection 34a of an operator 36, by spectrum 34b, and/or video monitoring 34c. The optical data stream may also be processed by a photodectector to monitor intensity, or any suitable device to convert the optical data stream to a digital data stream adapted for use by a computer 38. The optical data stream may also be processed by a photodectector 34d to monitor intensity, or any suitable device to convert the optical data stream to a digital data stream adapted for use by a computer 38.

To construct the array the operator 36 and/or computer 38 will adjust the beam altering optical element 22 to direct the movement of each optical trap to acquire the selected probe and contain it. The plurality of optical traps with contained probes form the composition of the configured array that may be reconfigured as to the composition or position of the probes depending on the needs of the user.

One example of an application of the system illustrated in FIG. 3 is to troll the probes through the media 3000 (FIG. 1) containing the targets T1-T5. (FIG. 1) By containing the probes optically, as opposed to physically, and moving the probes within the subject cell 10 the opportunity for interaction of a probe with each target is increased thus improving the speed and efficiency of the assay.

Another example of an application of the system illustrated in FIG. 3 is that upon completion of the assay selection can be made, via computer 38 and/or operator 36, of which probes to discard and which to collect. The re-configurable nature of the array allows for selective movement of a given optical trap and contained probe. In some cases the media 3000 and unbound targets will be removed or flushed from the subject cell 10 through an outlet port 18 and the assay will be completed. In other cases at least some of the probes still contained by optical traps, are reused with additional targets to perform further assays. This technique can be useful in the case of probes that tested positive or negative, depending on the parameters of the assay. In yet other cases, because the array of probes is re-configurable

as to the quantity and quality of probes forming the array, the optical traps can be used to discard unbound probes and acquire additional probes for further experimentation.

Another example of an application of the system illustrated in FIG. 3 is to interrogate cells by spectrum and create an array of probes from selected interrogated cells. Spectroscopy of a sample of biological material can be accomplished with an imaging illumination 39 suitable for either inelastic spectroscopy or polarized light back scattering, the former being useful for assessing chemical structure, and the later being suited for measuring nucleus size. For instance, a computer 38 can be used to analyze the spectral data and to identify suspected cancerous, pre-cancerous and/or non-cancerous cells and direct optical traps to contain selected cell types. The contained cells may then be used as the probes in further assays such as the interaction of other biological material, cells, antibodies, antigens, drugs or chemicals on the probes. Those skilled in the art will recognize that the methodology used to interrogate and concentrate cells based on parameters specific to cancerous cells, may be altered, without departing from the scope of the invention, for use with interrogating and/or separating blastomeres, cells, or other material as called out for in the protocol of an assay.

Another example of an application of the system illustrated in FIG. 3 is for investigating targets by spectrum. The spectrum of those probes which had positive results (have bound targets) can be obtained by using imaging illumination 39 such as that suitable for either inelastic spectroscopy or polarized light back scattering. The computer 38 can analyze the spectral data to identify the desired targets and direct the optical array to segregate those desired targets. Those skilled in the art will recognize that the methodology used to segregate targets based on spectral data may be altered, without departing from the scope of the invention, to identify and/or segregate targets based on other information obtainable from the targets and/or the optical data stream. The wavelengths of the laser beam 100 used to form arrays for investigating biological material include the infrared, near infrared, visible green, visible red, and visible blue from about 400nm to about 1.06.mu.m

An additional example of an application of the array is the use of a static, transmissive beam altering optical element to direct the array. The static beam altering optical element 40, such as a hologram or grating, as illustrated in FIG. 4 can be used to form a pre-determined range of optical traps. Using the static beam altering element 40 in situations where limited movement and/or reconfiguration of the array is adequate has the advantage of not requiring the computer processing power necessary to calculate the varying phase pattern available

with a dynamic beam altering optical element. Although the static transmissive beam altering optical element illustrated in FIG. 4 is shown with a fixed surface 41 and discreet regions 42-46, a static beam altering optical element, either transmissive or reflective, may also have a substantially continuously varying non-homogeneous surface, or a combination of discreet regions, and substantially continuously varying regions.

The movement of the probes 500-502 via the sequential creation of sets of optical traps is illustrated in FIGS. 5A and 5B. In some instances a simple movement of the array of probes, in a linear fashion within a media, can be accomplished by transferring the probes from a first set of optical traps to a second set. The first set of optical traps is generated by directing a laser beam at region one 42 of the beam altering optical element 40, which in-turn will produce beamlets emanating from region one 42 when passing through a focusing lens and form a set of optical traps at position one P1 containing the probes 500-503.

To move the probes 500-502 from position one P1 to position two P2, the static beam altering optical element 40 is rotated around a spindle 47 (which may be attached to a controlled motor (not shown) to align the laser beam with region two 43 which will generate the second set of optical traps at position two P2. By constructing the second set of optical traps in the appropriate proximity to the former location of the first set of optical traps the probes can be passed from set of optical traps to set of optical traps. The sequence may continue passing the probes from position two P2 to position three P3, from position three P3 to position four P4, and from position four to position five P5 by the rotation of the beam altering optical element to align the appropriate region 42-46 corresponding to the desired position P1-P5. The time interval between the termination of one set of optical traps and the generation of the next should be adequate to allow passage of the te to probes before they drift. One use of this system, as described within, is to troll the probes through the media thereby providing opportunity to have targets within the media interact with the probes. This type of simple movement may also be useful in moving the probes from a sub-cell 16 (FIG 1) to another area of the subject cell 10, or segregating probes into a sub-cell 16.

Shown in FIG. 5B is a staggered movement of the probes from a wide to narrow proximity. The staggered movement of the probes occurs in a similar fashion as described in reference to FIG. 5A. However, region one 42 now produces staggered optical traps thereby placing some probes 500 and 502 at position one P1 while at the same time placing another probe 501 at position two P2. As the probes are passed from set of optical traps to set of

optical traps position one P1 to position two P2 and so forth to position five P5 and position six P6, the staggered arrangement of the probes allows the probes to be packed densely without placing a set of traps in too close a proximity to two probes at the same time which could cause the probes to be contained by the wrong optical trap.

In some embodiments, it is not necessary to generate beamlets from each region of the static beam altering optical element 40, or move the beam altering optical element 40 in a set direction. Instead, changing the order of the regions will change the location of the sets of optical traps or the direction of the probes.

The above described method and system lends itself to a semi-automated or automated process through which the assay may be monitored, via video camera, spectrum, or an optical data stream which provides the computer controlling the selection of probes and generation of optical traps information useful to adjusting the quality of the probes contained by the optical traps and the composition of the probes forming the array.

Shown in FIG. 6A is the component view of a compact system for forming the optical traps, generally designated 50. The beam altering optical element 51, in this embodiment, is a dynamic optical element, with a reflective surface, which is also a phase only spatial light modulator such as the "PAL-SLM series X7665," manufactured by Hamamatsu of Japan or the "SLM 512SA7" manufactured by Bolder Nonlinear Systems of Lafayette, Colorado. Either of these dynamic optical elements is computer controlled.

To form a compact system for forming the optical traps, the optical element 51 is aligned with, or attached to, a housing 52 through which a first light channel 53a is provided. One end 53b of the first light channel is in close proximity to the optical element 51, the other end 53c of the first light channel communicates with a second light channel 53d formed perpendicular thereto. The second light channel is formed within the base 54a of the microscope lens mounting turret or "nosepiece" 54b. The nosepiece 54b in this embodiment is adapted to fit into a Nixon TE 200 series microscope. The second light channel communicates with a third light channel 53e which is also perpendicular to the second light channel. The third light channel 55a traverses from the top surface of the nosepiece 54b through the base of the nosepiece 54a and is parallel to the objective lens 56. Interposed opposite the back aperture 57 of the focusing lens, which in this embodiment is an objective lens 56, is a dichroic mirror 58. Other components within the compact system for forming

the optical traps 50 include a first mirror M1, a first and second set of transfer optics TO1 and TO2, and a second mirror M2.

To generate the optical traps, a laser beam is directed through a fiber optic cable 150 out a collimator end 151 and reflected off the dynamic surface 59 of the optical element 51. The beam of light (not shown) exiting the collimator end 151 of the fiber optic 150 is defracted by the active surface 59 of the optical element 51 into a plurality of beamlets (not shown). The beamlets then reflect off the first mirror M1 through the first set of transfer optics TO1 down the first light channel 53a through the second set of transfer optics TO2 to the second mirror M2; and are directed at the dichroic mirror 58 up to the back aperture 57 of the objective lens 56, are converged through the objective lens 56, thereby producing the optical gradient conditions necessary to form the optical traps.

That portion of the light which is split through the dichroic mirror 58, for imaging, passes through the lower portion of the third light channel 55b forming an optical data stream (not shown).

Shown in FIG. 6B is a representational drawing of a Nixon TE 200 series microscope into which the compact system for forming the optical traps 50 has been mounted, generally designated 60. The nosepiece 54 with the attached a housing 52 fits directly into the microscope via the mount (not shown) for the nosepiece 54a and 54b. The housing and its contents and attached optical element 51 are secured to the nosepiece 54a and 54b require few or no alterations or modifications to the remainder of the microscope.

For imaging, an illumination source 61 may be provided above the objective lens 56. Although the first and second set of transfer optics TO1 and TO2 are shown containing two lens elements each. Different and varying types and quantity of lens such symmetrical as air spaced singlets, symmetrical air spaced doublets and/or additional lens or groups of lens, such a lens placed in a telephoto configuration, can be chosen to achieve the image transfer from the first mirror M1 to the second mirror M2.

Since certain changes may be made in the above systems apparatus and methods without departing from the scope of the invention herein involved, it is intended that all matter contained in the above description, as shown in the accompanying drawing, the specification, and the claims shall be interpreted in an illustrative, and not a limiting sense.